| G   | C527   |                           | Constructing<br>Proteins<br>Estell et al.          | Humans & Me<br>g, Identifying &                               | thods for<br>Producing Such |                         |   |            |                   | Mutant Proteins day Mutant Proteins den Response in Human Constructions | ving Lower Allergenic<br>ving Methods for<br>ans & Methods for<br>ans fifting & Producing Such<br>antifring & |             |       |   |    |
|-----|--|---------------------------|--|---|-----------------------------|-------------------------|---|------------|-------------------|---|---|-------------|-------|---|----|
| -   |  |                           | SN# 09/062   | •   |                             |                         |   |            |                   | Mutant Prov. Human<br>Response in Human<br>Response incling, Iden       | ntifying  |             |       |   |    |
|     |  | <u>-</u> 0                | Met<br>ATG   | 2/15<br>eca<br>800<br>800                                     | Asp<br>GAT                  | Gin                     | Val<br>GTA  |            |                   | Consult<br>Proteins<br>Estell et al.<br>SN# 09/062,87                   | 12  |             |       |   |    |
|     |  | r Ser                     | Thr MA   | Asp Al  | Glu As<br>GAA G             | Ser G<br>TCT C          | Lys V.<br>AAG G   |            |                   | SN# (D)   | 1115  |             |       |   |    |
|     | -107<br>Met<br>GTG                           | Ser Thr<br>AGC ACA        | Ser Th<br>AGC AC                                   | Val As<br>GTA G/  | Glu Gl<br>GAA G             | His SE<br>CAC TO        | Leu Ly<br>TTA Av  |            | GC5 <sup>21</sup> |   |   |             |       |   | ·. |
|     |  | Gly Se                    | -60<br>Met Se<br>ATG AC                            | Tyr<br>TAT G  | -10<br>Val GI<br>GTT G      | Leu H<br>CTG C          | Asp Le<br>GAT T   | Ç          | +                 |   | `   |             |       |   |    |
|     | ATAAA  |                           | Thr MA   | Lys Ty<br>AAA TV  | Tyr V.                      | Ala Li<br>GCT C         | Pro A   | ·          | ·                 |   |   |             |       |   |    |
|     | S<br>SAGG/                                   | Ala Phe<br>GCG TTC        | Gin Th   | Phe Ly  | Ala T)<br>GCT T             | Pro A<br>CCT G          | His P<br>CAT C  |            | 4                 | 五   |   |             |       |   |    |
|     | RB:  | Met Al<br>ATG G           | Lys<br>AAA C                                       | Gin Pi  | Val A<br>GTC G              | Ala P<br>GCC C          | Ser H<br>TCT C  |            | 684               | Mean  |   |             |       |   |    |
|     | 5<br>  P   P   P   P   P   P   P   P   P   P | Thr MA                    | Phe Ly   | Lys G<br>AAG C  | Ser V                       | Lys A                   | Ser S<br>TCT T  |            |                   |   |   |             |       |   |    |
|     | ATGAA  | Phe T                     | Gly P  | Gin L   | Pro S<br>CCG A              | lle L<br>ATT            | Asp S   | //         | × (8)             |   | N THE   |             | •     |   | :  |
|     | GCAA   | -90<br>lle P<br>ATC T     | val<br>GTC   | Val G   | Asp F                       | 10<br>Gin<br>CAA        | lle A   |            | BRAT SHA          |   | Ar Ar   |             |       |   |    |
|     | ATTCT  | Leu II                    | ۵۲   |   | Lys<br>AAA 0                | Ser<br>TCA              | Gly<br>GGT  |            | 182               |   | A   |             |       |   |    |
|     | беп  | Ala L                     | PRO<br>Tyr #<br>TAT A                              | Gly Lys<br>GGG AAA  | Lys                         | Val<br>GTA              | Ser<br>AGC  | <b>1</b> - |                   |   |   | } . \       |       |   |    |
|     | 4<br>CTATT                                   | Leu                       | Lys  | Gly<br>GGC  | Leu                         | Gly<br>GGC              | Asp<br>GAC  | 1B         |                   |   | f   |             | 4     |   |    |
|     | гстат  | Ala<br>GCT                | -70<br>Lys<br>AAG                                  | Lys<br>AAA  | -20<br>Glu<br>GAA           | Tyr<br>TAC              | lle<br>ATC  |            |                   |   |   | MART<br>SKD |       |   |    |
|     | ATAA1  | Phe                       |  |   |                             |                         | 30<br>Val<br>GTT  | FIG.       |                   |   |   |             | FIG   |   |    |
|     | CAGA   |                           | Gly Glu<br>GGG GAA                                 | Ser Glu<br>TCT GAA  | Ala Val Lys<br>GCT GTA AAA  | Val Pro<br>GTG CCT      | Ala<br>GCG  | 4          |                   |   |   |             |       |   |    |
|     | ATACA  | PRE<br>Leu Leu<br>TTG CTG | Asn  | lle<br>ATT  | Ala<br>GCT                  | Ser                     | Val<br>GTA  |            |                   |   |   | TIN THE     |       |   |    |
|     | 3<br><b>←</b><br>&TT&                        | Ser<br>AGT                | Ser<br>TCA   | Val<br>GTC  | Lys                         | 1<br>Ala Gin<br>GCG CAG | Lys<br>AAA  |            |                   |   |   | Clarpour    | Or /  |   |    |
|     | ATACA  | -100<br>lle<br>ATC        | Lys<br>AA  | -50<br>Asp<br>GAT   | Glu                         | 1<br>Ala<br>GCG         | Val<br>GTT  |            |                   |   |   | 0 /         |       | 1 | ;  |
| s.' | TACT!  |                           | Gly<br>GGG   | ς<br>AA<br>AA   | Asn                         | Ala Tyr<br>GCG TAC      | Asn<br>AAT  |            |                   |   |   |             | PRE   |   |    |
|     | TCCA   | Val Trp<br>GTA TGG        | Ala<br>GCA   | Lys<br>AAG  | Thr Leu<br>ACA TTA          | Ala<br>GCG              | Ser<br>TCA  |            |                   |   |   | c           | HESSE | 1 |    |
|     | ATTA   | Lys<br>AAA                | Gin Ala Ala Gly Lys Ser<br>CAG GCG GCA GGG AAA TCA | -50<br>Ser Ala Ala Lys Lys Asp<br>AGC GCC GCT AAG AAG AAA GAT | Thr<br>ACA                  | Ala His<br>GCA CAT      | Thr Gly Ser Asn Val Lys Val Ala Val ACT GGA TCA AAT GTT AAA GTA GCG GTT |            |                   |   |   |             | 70    |   |    |
|     | <b>9</b>                                     | Gly Lys<br>GGC AAA        | Gin  | Ata<br>GCT  | Ala<br>GCT                  | Ala<br>GCA              | Thr   |            |                   |   |   |             | 蓝岩    | V |    |
|     | YACT.  | Giy<br>GGC                | -80<br>Ala<br>GCC                                  | Ala<br>GCC  | -30<br>Ser<br>TCA           | Val<br>GTA              | Tyr<br>TAC  |            |                   | 4.  | •   |             | ECO   |   |    |
|     | 5<br><b>→</b><br>GGTO                        | Arg<br>AGA                | Ser<br>TCT   | Ser<br>AGC  | Ala<br>GCT                  | His<br>CAC              | 20<br>Gly<br>GGC  |            |                   |   |   |             |       |   | •  |
|     | -  | 66                        | 174  | 249   | 324                         | 399                     | 474   | 1          |                   |   | e.  |             |       |   |    |

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Mutant Proteins Having Lower Allergenic Response in Humans & Methods for Constructing, Identifying & Producing Such Proteins Estell et al. SN# 09/062,872s GC527 821 3/15 Gly Pro GGA CCT 9 9 9 9 oca GCA A A C Asn Val Gly Tyr Pro ( ATG Met \$<del>\$</del> Ala Val GIY ASN LYS TYY GIY AIA TYY GGA AAC AAA TAC GGG GCG TAC gCC GCC Ala Ash Ash GCA AAC AAT Ser Val AGC GTA ( Ala Val I GCT GTA HIS GIV THY HIS VAI V. CAC GGA ACT CAC GTT ( ASP LYS GAT AAA Ser TCA Leu Tyr CTT TAC ASN GIV IIE GIU TTP AIA IIE ASC GGA ATC GAG TGG GCG ATC 1 1 1 1 1 1 1 160 Ser Ser Thr Gly Ser CA AGC ACA GGC AGC TCA AGC ACA Ala Ala Val GCG GCA GTT ( 15t 1C1 Ser Ala Ala Ser GCA TCA Gin Arg Ala E CAA AGA GCA 1 Ser TCT Ala Pro Ser I Ala Ala Leu Lys A Asp Ser Ser Asn C GAC AGC AGC AAC C Thr Ser TCC 60 Asp GAC GIU GIY Thr GAA GGC ACT GGC GTT ( /a Ser Thi CAA CAA FE Phe TC ser 101 GIY GIN TYR SER TRP IIE GGC CAA TAC AGC TGG ATC 80 Val Leu Gly Val TTA GGT GTA TTA Asn Pro CCT 66.6 8 2 E Ala Ala Ala Gly Asn GCG GCA GCC GGT AAC Pro ' GIU Thr Ash F GAA ACA AAT C Ser TCT Val Gly Ala V 65 Met Ser Leu Gly Gly Pro ATG AGC CTC GGC GGA CCT arc Arc ase 1CA Pro Ser CCT TCT Leu Ash Ash . Ser 100 雪哥 150 雪岩 95 95 159 310 Ser Met \ je Naj Ala Asp GAC Ala Ala GCG GCT Val Asn Asp GCT Gy Val Ala Gly Gly Ala S GCA GGC GGA GCC A ATE ATE GG1 雪岩 雪島 35 Ş Ser 100 阜 120 Asp GAC 18 ES ද ල්ලි ව

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O 18-Ala Gly Ala Ala ta

Leu lle TTG ATT

Ala GCT

230 Ala

AC.

Leu Ser Lys His Pro Ash Trp Thr Ash CTT TCT AAG CAC CCG AAC TGG ACA AAC

13 Pro 210

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CAA AGC ACG CTT

Ser lle TCT ATC

Gly Val

200 Ala GCA 1

Met ATG

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35

Glu GAG

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SCA GCA

Val le GTC ATT

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873

4¥ AC

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849

669

624

549

924

Ser . Thr

Pro His Val 1 CCG CAC GTT C

Met Ala Ser ATG GCA TCT

Sec

220 Thr

ACG TCA

1316 ATAATCGACGGATGGCTCCCTCTGAAAATTTTAACGAGAGAGGGGGGTTGACCCGGCTCAGTCCCGTAACGGCCAAGTCCTGAAACGTCTCAATCGCCG TERM
270
270
Val Gin Ala Ala Ala Gir AA AACATAAAAACCGGCCTTGGCCCCGCGGTTTTTTATTTTCTTCCTCCGCATGTTCAATCCGCTCC
1224 GTA CAG GCG GCA GCT CAG TAA AACATAAAAACCGGCCTTGGCCCCGCGGTTTTTTATTTTCTTCCTCCGCATGTTCAATCCGCTCC IN ASS SUBCLASS APPRIONE 1 (1. G. F16. DRAFTSHAN

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1416 CTICCCGGTTTCCGGTCAGCTCAATGCCGTCGGCGCGCGTTTTCCTGATACCGGGAGGCGGCATTCGTAATCGGATC

FIG.-1B-3



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## CONSERVED RESIDUES IN SUBTILISINS FROM BACILLUS AMYLOLIQUEFACIENS

| 1<br>A  | Q      | s | v | P | • | G | • | • | 10              | •             | • | A | P | A | • | н | • | •  | 20<br>G         |
|---------|--------|---|---|---|---|---|---|---|-----------------|---------------|---|---|---|---|---|---|---|----|-----------------|
| 21      | T      | G | s | • | v | ĸ | v | A | 3 (<br>V        | •             | D | • | G | • | • | • | • |    | 40<br>P         |
| 41<br>D | L      | • | • | • | G | G | A | s | 50              | v             | P | • | • | • | • | • | • | Q  | 60<br>D         |
| 61      | N      | • | н | G | T | н | v | A | 7 (<br>G        | T             | • | A | A | L | N | N | s | I  | 80<br>G         |
| 81<br>V | L      | G | v | A | P | s | A | • | 9(<br>L         | Y             | A | v | ĸ | v | L | G | A |    | G               |
| 10<br>S | 1<br>G | • | • | s | • | L | • |   | 11(<br>G        |               | E | W | A | • | N | • | • |    |                 |
| 12<br>V | 1      | N | • | s | L | G | • | P | 13(<br>S        |               | s | • | • | • | • | • | A |    | L <b>4</b> 0    |
| 14      | 1      | • | • | • | G | v | • | v | 150<br>V        | )<br>A        | A | • | G | N | • | G | • |    |                 |
| 16      | 1      | • | • | • | • | Y | P | : | 170             | )<br>Y        | • | • | • | • | A | v | G | A  |                 |
| 18<br>D | 1      | • | N | • | • | A | s | F | 19(<br>S        |               | • | G | • | • | L | D | • |    | 200<br><b>A</b> |
| 20<br>P | 1<br>G | v | • | • | Q | s | T |   |                 |               |   |   |   |   |   |   |   | G  | 220<br>T        |
| 22<br>S | 1<br>M | A | • | P | н | v | A | G | 23(<br><b>A</b> | 0<br><b>A</b> | A | L | • | • | • | ĸ | • |    | 240             |
| 24<br>W |        | • | • | Q | • | R | • |   | 25<br>L         |               |   |   | • | • | • | L | G |    | 260             |
| 26      |        | Y | G | • | G | L |   |   | 27              |               | Α | A | • | • |   |   | F | IC | ā2              |

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COMPARISION OF SUBTILISIN SEQUENCES FROM:

B.amyloliquefaciens

B.licheniformis

B.lentus

B.subtilis

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4444 I H S SSAF 200 0000 SSHF 9 > > > >> Ö Z SAS G C H × O O G 9 9 9 K **S** A Z 0 K × 0 × K S > SH 9999 01 K KK

000 HH SES ZZ Z ZOZ 7 K K H > G G 4 FF HH O 00 HH H 8 8 8 8 ZSZZ ZUU Ö Ω 999 a a H Ø # H Z S ZXA K . 西田田田 8 6 6 D4 D4 D4 S SS KKK 00 Ö 00 C H Z コココ 9999

Σ X G C Z Z SE Z Ü 3 3 F 回回 G Ç C S Q 30 S S S S S Ö C 100 G S S Ö G E S A S S A Z 11 H H S S M S Д > C C > >

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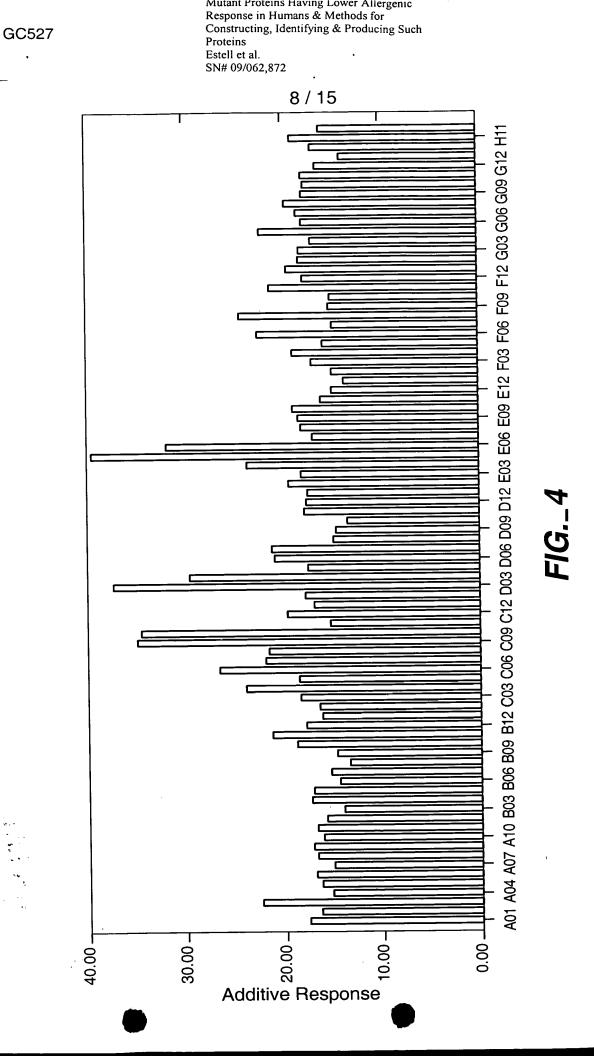
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ZHZS þ 4 HHZ X X X X 8 8 8 B ひしひと AA K K KK G G C C H Д SESE AA **EZZZ** 220 220 11 S 11 S 11 S S  $\infty$ 8 C ZZ H A H S ZUZU O U 21 P Q, **KKFF** H H H H 8 8 8 8  $aa \times a$ G S K > O Ö 201 P G P G P G Ü G

9998 KKH 270 C O C O Z 1111 00 Ü XXS G C E E Z DZSS O 000 コココ **HHH** HKKK 8 8 8 8 zooz 国区の区 ち段取用 SUZZ 我我我我 > > > H a a a a F & 50 > ZKZ F F 8 8 241 3 43 3



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APPTOVICE C.C. FIG.

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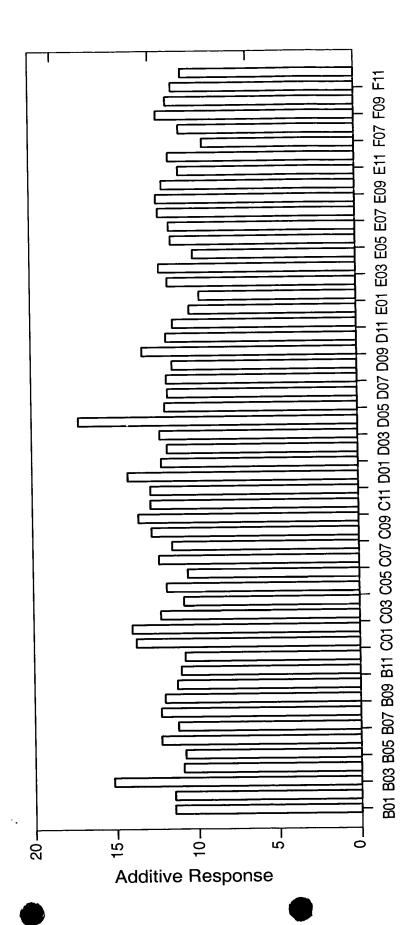


FIG.\_5

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D4

**D3** 

D2

D1

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| 116.      | SUBCLASS |           |
|-----------|----------|-----------|
|           | 7.7.55 5 |           |
| APPLIEVED | A-52     | DRAFTSHAN |

| 1  | A12       | IKDFHVYFRESRDAG        | 49 | E12 | SATSRGVLVVAASGN          |
|----|-----------|------------------------|----|-----|--------------------------|
| 2  | A11       | LEQAVNSATSRGVLV        | 50 | E11 | SRGVLVVAASGNSGA          |
| 3  | A10       | AQSVPWGISRVQAPA        | 51 | E10 | VLVVAASGNSGAGSI          |
| 4  | A10       | VPWGISRVQAPAAHN        | 52 | E 9 | VAASGNSGAGSISYP          |
| 5  | A9<br>A8  | GISRVQAPAAHNRGL        | 53 | Ē8  | SGNSGAGSISYPARY          |
| 6  | A8<br>A7  | RVQAPAAHNRGLTGS        | 54 | E7  | SGAGSISYPARYANA          |
| 7  |           | APAAHNRGLTGSGVK        | 55 | Ē6  | GSISYPARYANAMAV          |
| 8  | A6        | AHNRGLTGSGVKVAV        | 56 | E5  | SYPAR <u>YANAMAVGA</u> T |
| 9  | A5        | RGLTGSGVKVAVLDT        | 57 | E4  | ARYANAMAYGATDON          |
| 10 | A4        | TGSGVKVAVLDTGIS        | 58 | E3  | ANAMAVGATDQNNNR          |
| 11 | A3        | GVKVAVLDTGISTHP        | 59 | E2  | MAVGATDQNNNRASF          |
| 12 | A2        | VAVLDTGISTHPDLN        | 60 | Ē1  | GATDQNNNRASFSQY          |
| 13 | A1<br>B12 | LDTGISTHPDLNIRG        | 61 | F12 | DONNNRASFSQYGAG          |
| 14 | B12       | GISTHPDLNIRGGAS        | 62 | F11 | NNRASFSQYGAGLDI          |
| 15 | B10       | THPDLNIRGGASFVP        | 63 | F10 | ASFSQYGAGLDIVAP          |
| 16 |           | DLNIRGGASFVPGEP        | 64 | F9  | SQYGAGLDIVAPGVN          |
| 17 | B9        | IRGGASFVPGEPSTQ        | 65 | F8  | GAGLDIVAPGVNVQS          |
| 18 | B8<br>B7  | GASFVPGEPSTQDGN        | 66 | F7  | LDIVAPGVNVQSTYP          |
| 19 | B6        | FVPGEPSTQDGNGHG        | 67 | F6  | VAPGVNVQSTYPGST          |
| 20 | B5        | GEPSTQDGNGHGTHV        | 68 | F5  | GVNVQSTYPGSTYAS          |
| 21 |           | STODGNGHGTHVAGT        | 69 | F4  | VQSTYPGSTYASLNG          |
| 22 | B4<br>B3  | DGNGHGTHVAGTIAA        | 70 | F3  | TYPGSTYASLNGTSM          |
| 23 | B2        | GHGTHVAGTIAALNN        | 71 | F2  | GSTYASLNGTSMATP          |
| 24 | -B1       | THVAGTIAALNNSIG        | 72 | F1  | YASLNGTSMATPHVA          |
| 25 | C12       | AGTIAALNNSIGVLG        | 73 | G12 | LNGTSMATPHVAGAA          |
| 26 | C12       | IAALNNSIGVLGVAP        | 74 | G11 | TSMATPHVAGAAALV          |
| 27 | C10       | LNNSIGVLGVAPSAE        | 75 | G10 | ATPHVAGAAALVKQK          |
| 28 | C10       | SIGVLGVAPSAELYA        | 76 | G9  | HVAGAAALVKQKNPS          |
| 29 | C8        | VLGVAPSAELYAVKV        | 77 | Ğ8  | GAAALVKQKNPSWSN          |
| 30 | C7        | VAPSAELYAVKVLGA        | 78 | G7  | ALVKQKNPSWSNVQI          |
| 31 | C6        | SAELYAVKVLGASGS        | 79 | G6  | KQKNPS <u>WSNVOIRNH</u>  |
| 32 | C5        | LYAVKVLGASGSGSV        | 80 | G5  | NPS <u>WSNVOIRNH</u> LKN |
| 33 | C4        | VKVLGASGSGSVSSI        | 81 | G4  | WSNVQIRNHLKNTAT          |
| 34 | C3        | LGASGSGSVSSIAQG        | 82 | G3  | VQIRNHLKNTATSLG          |
| 35 | C2        | SGSGSVSSIAQGLEW        | 83 | G2  | RNHLKNTATSLGSTN          |
| 36 | C1        | GSVSSIAQGLEWAGN        | 84 | G1  | LKNTATSLGSTNLYG          |
| 37 | D12       | SSIAQGLEWAGNNGM        | 85 | H12 | TATSLGSTNLYGSGL          |
| 38 | D11       | AQGLEWAGNNGMHVA        | 86 | H11 | SLGSTNLYGSGLVNA          |
| 39 | D10       | LEWAGNNGMHVANLS        | 87 | H10 | STNLYGSGLVNAEAA          |
| 40 | D9        | <b>AGNNGMHVANLSLGS</b> | 88 | Н9  | NLYGSGLVNAEAATR          |
| 41 | D8        | NGMHVANLSLGSPSP        |    |     |                          |
| 42 | D7        | HVANLSLGSPSPSAT        |    |     |                          |
| 43 | D6        | NLSLGSPSPSATLEQ        | •  |     |                          |
| 44 | D5        | LGSPSPSATLEQAVN        |    |     |                          |
| 45 | 53        | DCDCATT.FOAVNSAT       |    |     |                          |

**PSPSATLEQAVNSAT** 

SATLEQAVNSATSRG

LEQAVNSATSRGVLV

**AVNSATSRGVLVVAA** 

FIG.\_6A

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|          |            |                                 |                  |     | WALL DATE NI CICCODE |
|----------|------------|---------------------------------|------------------|-----|----------------------|
| 1        | A12        | IKDFHVYFRESRDAG                 | 49               | E12 | KKIDVLNLSIGGPDF      |
| 2        | A11        | DAELHIFRVFTNNQV                 | 50               | E11 | DVLNLSIGGPDFMDH      |
| 3        | A10        | PLRRASLSLGSGFWH                 | 51               | E10 | NLSIGGPDFMDHPFV      |
| 4        | A9         | RASLSLGSGFWHATG                 | 52               | E9  | IGGPDFMDHPFVDKV      |
| 5        | A8         | LSLGSGFWHATGRHS                 | 53               | E8  | PDFMDHPFVDKVWEL      |
| 6        | A7         | GSGFWHATGRHSSRR                 | 54               | E7  | MDHPFVDKVWELTAN      |
| 7        | A6         | FWHATGRHSSRRLLR                 | 55               | E6  | PFVDKVWELTANNVI      |
| 8        | A5         | ATGRHSSRRLLRAIP                 | 56               | E5  | DKVWELTANNVIMVS      |
| 9        | AS<br>A4   | RHSSRRLLRAIPRQV                 | 57               | E 4 | WELTANNVIMVSAIG      |
| 10       |            | SRRLLRAIPRQVAQT                 | 58               | E3  | TANNVIMVSAIGNDG      |
|          | A3         | LLRAIPROVAOTLQA                 | 59               | E2  | NVIMVSAIGNDGPLY      |
| 11<br>12 | A2<br>A1   | AIPRQVAQTLQADVL                 | 60               | E1  | MVSAIGNDGPLYGTJ      |
|          | B12        | ROVAQTLQADVLWQM                 | 61               | F12 | AIGNDGPLYGTLNNP      |
| 13       |            | AQTLQADVLWQMGYT                 | 62               | F11 | NDGPLYGTLNNPADQ      |
| 14       | B11        | LQADVLWQMGYTGAN                 | 63               | F10 | PLYGTLNNPADQMDV      |
| 15       | B10        | DVLWQMGYTGANVRV                 | 64               | F9  | GTLNNPADQMDVIGV      |
| 16       | B9         | WOMGYTGANVRVAVF                 | 65               | F8  | NNPADOMDVIGVGGI      |
| 17       | B8<br>B7   | GYTGANVRVAVFDTG                 | 66               | F7  | ADOMDVIGVGGIDFE      |
| 18       |            | GANVRVAVEDIG<br>GANVRVAVEDTGLSE | 67               | F6  | MDVIGVGGIDFEDNI      |
| 19       | B6         | VRVAVFDTGLSEKHP                 | 68               | F5  | IGVGGIDFEDNIARF      |
| 20       | B5         | AVFDTGLSEKHPHFK                 | 69               | F4  | GGIDFEDNIARFSSR      |
| 21       | B4         | DTGLSEKHPHFKNVK                 | 70               | F3  | DFEDNIARFSSRGMT      |
| 22       | B3         |                                 | 71               | F2  | DNIARFSSRGMTTWE      |
| 23       | B2         | LSEKHPHFKNVKERT                 | 72               | F1  | ARFSSRGMTTWELPG      |
| 24       | B1         | KHPHFKNVKERTNWT                 | 73               | G12 | SSRGMTTWELPGGYG      |
| 25       | C12        | HFKNVKERTNWTNER                 | 7 <i>3</i>       | G11 | GMTTWELPGGYGRMK      |
| 26       | C11<br>C10 | NVKERTNWTNERTLD                 | 75               | G10 | TWELPGGYGRMKPDI      |
| 27       |            | ERTNWTNERTLDDGL                 | 75<br>76         | G9  | LPGGYGRMKPDIVTY      |
| 28       | C9         | NWTNERTLDDGLGHG                 | 77               | G8  | GYGRMKPDIVTYGAG      |
| 29       | C8         | NERTLDDGLGHGTFV                 | 7 <i>1</i><br>78 | G7  | RMKPDIVTYGAGVRG      |
| 30       | C7         | TLDDGLGHGTFVAGV                 | 76<br>79         | G6  | PDIVTYGAGVRGSGV      |
| 31       | C6         | DGLGHGTFVAGVIAS                 | 80               | G5  | VTYGAGVRGSGVKGG      |
| 32       | C5         | GHGTFVAGVIASMRE                 |                  | G4  | GAGVRGSGVKGGCRA      |
| 33       | C4         | TFVAGVIASMRECQG                 | 81<br>82         | G3  | VRGSGVKGGCRALSG      |
| 34       | C3         | AGVIASMRECQGFAP                 |                  | G2  | SGVKGGCRALSGTSV      |
| 35       | C2         | IASMRECQGFAPDAE                 | 83               | G1  | KGGCRALSGTSVASP      |
| 36       | C1         | MRECQGFAPDAELHI                 | 84               | H12 | CRALSGTSVASPVVA      |
| 37       | D12        | CQGFAPDAELHIFRV                 | 85               | H11 | LSGTSVASPVVAGAV      |
| 38       | D11        | FAPDAELHIFRVFTN                 | 86               |     | TSVASPVVAGAVTLL      |
| 39       | D10        | DAELHIFRVFTNNQV                 | 87               | H10 | ASPVVAGAVILL         |
| 40       | D9         | LHIFRVFTNNQVSYT                 | 88               | H9  | VVAGAVTLLVSTVQK      |
| 41       | D8         | FRVFTNNQVSYTSWF                 | 89               | H8  |                      |
| 42       | D7         | FTNNQVSYTSWFLDA                 | 90               | H7  | GAVTLLVSTVQKREL      |
| 43       | D6         | NQVSYTSWFLDAFNY                 | 91               | H6  | TLLVSTVQKRELVNP      |
| 44       | D5         | SYTSWFLDAFNYAIL                 | 92               | Н5  | VSTVQKRELVNPASM      |
| 45       | D4         | SWFLDAFNYAILKKI                 | 93               | H4  | VOKRELVNPASMKQA      |
| 46       | D3         | LDAFNYAILKKIDVL                 | 94               | Н3  | RELVNPASMKQALIA      |
| 47       | D2         | FNYAILKKIDVLNLS                 | 95               | H2  | VNPASMKQALIASAR      |
| 48       | D1         | AILKKIDVLNLSIGG                 | 96               | H1  | ASMKQALIASARRLP      |
|          |            |                                 |                  |     |                      |

FIG.\_6B

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| 97  | I12        | IKDFHVYFRESRDAG |
|-----|------------|-----------------|
| 98  | 111        | DAELHIFRVFTNNQV |
| 99  | I 10       | KQALIASARRLPGVN |
| 100 | 19         | LIASARRLPGVNMFE |
| 101 | 18         | SARRLPGVNMFEQGH |
| 102 | 17         | RLPGVNMFEQGHGKL |
| 103 | 16         | GVNMFEQGHGKLDLL |
| 104 | 15         | MFEQGHGKLDLLRAY |
| 105 | Ĭ 4        | OGHGKLDLLRAYQIL |
| 106 | 13         | GKLDLLRAYQILNSY |
| 107 | 12         | DLLRAYQILNSYKPQ |
| 108 | <b>I</b> 1 | RAYQILNSYKPQASL |
| 109 | J12        | QILNSYKPQASLSPS |
| 110 | J11        | NSYKPQASLSPSYID |
| 111 | J10        | KPQASLSPSYIDLTE |
| 112 | J9         | ASLSPSYIDLTECPY |
| 113 | J8         | SPSYIDLTECPYMWP |
| 114 | J7         | YIDLTECPYMWPYCS |
| 115 | J6         | LTECPYMWPYCSQPI |
| 116 | J5         | CPYMWPYCSQPIYYG |
|     |            |                 |

FIG.\_6C

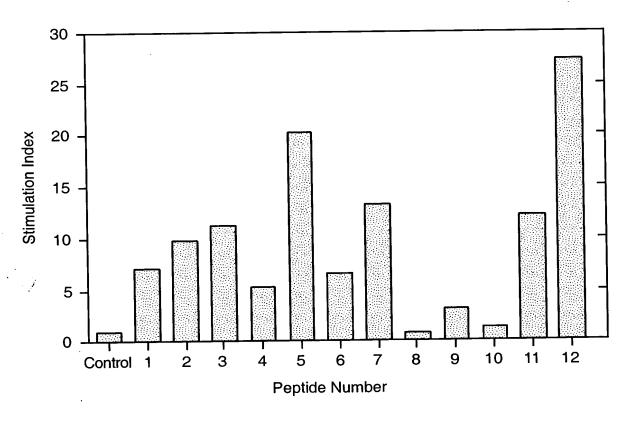


FIG.\_10

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IVTYGAGVRGSGVKGGCRALSGTSVASPVVAGAVTLLVSTVQKRELVNPASMKQALIASARRLPG VNMFEQGHGKLDLLRAYQILNSYKPQASLSPSYIDLTECPYMWPYCSQPIYYGGMPTVVNVTILN TANNVIMVSAIGNDGPLYGTLNNPADQMDVIGVGGIDFEDNIARFSSRGMTTWELPGGYGRMKPD TLQADVLWQMGYTGANVRVAVFDTGLSEKHPHFKNVKERTNWTNERTLDDGLGHGTFVAGVLASM AKARNSFISSALKSSEVDNWRIIPRNNPSSDYPSDFEVIQIKEKQKAGLLTLEDHPNIKRVTPQR KVFRSLKYAESDPTVPCNETRWSQKWQSSRPLRRASLSLGSGFWHATGRHSSRRLLRAIPRQVAQ RECQGFAPDAELHIFRVFTNNQVSYTSWFLDAFNYAILKKIDVLNLSIGGPDFMDHPFVDKVWEL MKLVNIWLLLLVVLLCGKKHLGDRLEKKSFEKAPCPGCSHLTLKVEFSSTVVEYEYIVAFNGYFT

FIG.\_7

J.EAHLGDPKPRPLPACPRLSWAKPQPLNETAPSNLWKHQKLLSIDLDKVVLPNFRSNRPQVRPL

SPGESGAWDIPGGIMPGRYNQEVGQTIPVFAFLGAMVVLAFFVVQINKAKSRPKRRKPRVKRPQL

TVASPAETESKNGAEQTSTVKLPIKVKIIPTPPRSKRVLWDQYHNLRYPPGYFPRDNLRMKNDPL DWNGDHIHTNFRDMYQHLRSMGYFVEVLGAPFTCFDASQYGTLLMVDSEEEYFPEEIAKLRRDVD NGLSLVIFSDWYNTSVMRKVKFYDENTRQWWMPDTGGANIPALNELLSVWNMGFSDGLYEGEFTL ANHDMYYASGCSIAKFPEDGVVITQTFKDQGLEVLKQETAVVENVPILGLYQIPAEGGGRIVLYG DSNCLDDSHRQKDCFWLLDALLQYTSYGVTPPSLSHSGNRQRPPSGAGSVTPERMEGNHLHRYSK

GMGVTGRIVDKPDWQPYLPQNGDNIEVAFSYSSVLWPWSGYLAISISVTKKAASWEGIAQGHVMI

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275 269 280 235 229 192 145 144 191 197 96 98 94 47 ----DVMAPGVSIQSTLPGNKYGAYNGTSMASPHVAGAAALIL ----DIVAPGVNVQSTYPGSTYASLNGTSMATPHVAGAAALVK VVVAAAGNEGTSGSSSTVGYPGKYPSVIAVGAVDSSNQRASFSSVGPEL-LVVAASGNSGA----GSISYPARYANAMAVGATDQNNNRASFSQYGAGL-IMVSAIGNDGP--LYGTLNNPADQMDVIGVGGIDFEDNIARFSSRGMTTW SVASPVVAGAVTLLV DGSGQYSWIINGIEWAIANNMDVINMSLGGPS-GSAALKAAVDKAVASGV SGSGSVSSIAQGLEWAGNNGMHVANLSLGSPS-PSATLEQAVNSATSRGV NQVSYTSWFLDAFNYAILKKIDVLNLSIGGPDFMDHPFVDKVWELTANNV SMVPSETNPFQDNNSHGTHVAGTVAALNNSIGVLGVAPSASLYAVKVLGA SFVPGEPST-QDGNGHGTHVAGTIAALNNSIGVLGVAPSAELYAVKVLGA AQSVPYGVSQ-IKAPALHSQGYTGSNVKVAVIDSGIDSSHPDLK-VAGGA AQSVPWGISR-VQAPAAHNRGLTGSGVKVAVLDTGI-STHPDLN-IRGGA --TNERTLDDGLGHGTFVAGVIASMRECQGF---APDAELHIFRVFTN - RAIPRQVAQTLQADVLWQMGYTGANVRVAVFDTGLSEKHPHFKNVKERT SKHPNWTNTQ----VRSSLENTTTKLGDSFYYGKGLINVQAAAQ QKNPSWSNVQ---IRNHLKNTATSLGSTNLYGSGLVNAEAATR STVQKRELVNPASMKQALIASARRLPGVNMFEQG----HGKL GCRALSGT GRMKPDIVTYGAGVRGSGVKG ELPGGY SAVINASE SAVINASE SAVINASE SAVINASE SAVINASE SAVINASE S2HSBT S2HSBT SZHSBT S2HSBT S2HSBT S2HSBT BPN'

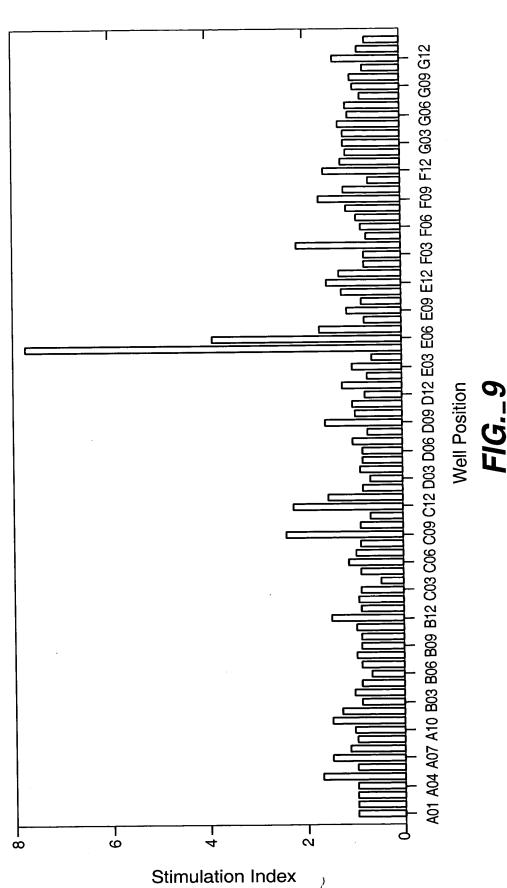
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